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Assessment of Iron Chelation Therapy Adherence in Patients with Thalassemia Major in Babylon Province

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Abstract:

BACKGROUND: Thalassemia is severe public health problem in Iraq and other nearby countries, represents about 75% of all hemogloniopathy with prevalence and incidence 36/100.000 and 34/100.000 respectively. beta thalassemia major represented 67% of all types of thalassemia. In the absence of treatment, it cause bony deformities and hepatosplenomegaly. Bone marrow transplant is the only curative treatment, but it is restricted to only a few patients. As a result, the majority of patients also receive iron chelation therapy along with routine blood transfusions. Failure of chelation can result in endocrinopathies, cardiomyopathy, and hepatic failure, iron chelation therapy requires careful monitoring and high adherence to obtain acceptable therapeutic outcomes. The main factor causing morbidity and mortality in thalassemia is iron excess. Adherence is a complicated phenomenon that involves interconnected elements linked to each patient's condition, therapy, and environment as well as psychological elements.

OBJECTIVE: We assessed the adherence to iron chelation therapy in thalassemia major patients in Babylon province in Iraq and trying to identify the factors leading to poor adherence.

MATERIALS AND METHODS: This is cross sectional study performed over the course of two months on 100 patients with β-thalassemia major registered at hereditary blood disease center, in Babylon, Iraq, using deferasirox as chelation agent by direct interview using a predesigned questionnaire.

RESULT: Mean age was (14.93± 6.85) years, (61%) of patients were males. The great majority (97%) were single. (59%) of patients were below bachelor. (96%) were unemployed and about half of patients (51%) were rural. Number of affected family members range from 0 to 4, with only one affected member rank one. (92%) of them not use chronic medication other than chelating therapy and folic acid. Disease complication other than organomegaly present in 14% of patients, that include hepatitis C infection, delayed growth, diabetes mellitus and hypothyroidism. More than three-quarters of patients (79%) have good adherence for chelation therapy, were 21 patients have poor adherence, mostly secondary to gastrointestinal side effect (nausea, vomiting, stomach discomfort and bitter taste), or non-specific causes (disinterest, forgetfulness, feeling hassled and taking other medication). The mean duration from diagnosis was 13.6 years, transfusion duration was 13.4 years, transfusion frequency was about 23 days and chelating duration was 10.7 years. Mean of packed cell volume (PCV) was 22%, while mean of serum ferritin was 4342mg/ dl. There was significant association between mean PCV of patients and their adherence to chelating therapy P value was (0.009), other variable show non-significant association.

CONCLUSION: Thalassemia major patients in Babylon governorate have good level of adherence to iron chelation therapy which was nearly comparable or even better than adherence rates in other Middle East countries. Despite that, the chelation is inadequate due to logistic issues.

Keywords:

Adherence, chelation, thalassemia

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Introduction

A blood condition known as thalassemia is characterized by a decreased production of the alpha or beta-hemoglobin chains.[1] In the nations of the Mediterranean, Middle East, Indian subcontinent, and South East Asia, it represents a serious public health issue.[2]

Thalassemia makes for around 75% of all hemoglobinopathies in Iraq. There were 36/100.000 cases per 100,000 people. The incidence, however, was 34/100.000 live births. Of all forms of thalassemia, thalassemia major was the most prevalent (67%).[3]

Two major events can be used to describe the disease's development. The first is anemia brought on by decreased globin synthesis. The second is the precipitation of excess α-chain leading to premature red blood cell destruction and hemolysis. On the contrary, in the absence of blood transfusion, anemia causes erythroid hyperplasia that will lead to bony deformities and extramedullary hematopoiesis with resultant hepatosplenomegaly.[4]

Depending on the clinical severity, thalassemia can be divided into transfusion-dependent thalassemia (TDT) and non-TDT.[5]

Currently, a bone marrow transplant is the only cure for thalassemia. Due to the high cost and lack of an HLA-matched donor, it is only available to a small number of patients. As a result, the standard of care for the majority of patients includes iron chelation therapy (ICT) in addition to routine blood transfusions. A comprehensive therapeutic approach is excellent for the therapy of a patient with TDT.[6]

To reduce inefficient erythropoiesis, the major goal of transfusion is to keep the mean hemoglobin level above 10 g/dL.[2]

Although there is minimal information on their efficacy, gene therapy and the use of erythropoiesis-improving substances such as activin receptor-II ligand traps and Janus kinase 2 inhibitors are promising treatments.[5]

Transfusions, however, have the potential to cause excessive systemic iron overload and iron accumulation in the heart, liver, spleen, and other organs, which can result in a number of serious consequences. Endocrinopathies, cardiomyopathies, and hepatic failure are some of these side effects. The main factor causing morbidity and mortality in thalassemia is iron overload.[1] Thus, iron chelation treatment is essential for treating posttransfusional iron overload.[7]

It has been demonstrated that iron-chelating drugs reduce organ damage and increase survival by forming a combination with iron that causes its excretion.[8]

For ICT to be effective, close supervision and strict adherence to the dosing schedule are essential.[5]

Deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX) are the three main iron chelation substances. Due to its poor oral bioavailability, DFO must be delivered subcutaneously or intravenously up to once per day, whereas DFP and DFX may be taken orally up to three times per day.[7]

A tridentate ligand with a strong affinity for iron is called DFX. Iron chelation is better suited to a once-daily regimen due to its lengthy half-life (11–19 h). The majority of it is broken down by bile and the rest by urine. It frequently interacts with other drugs, which could reduce bioavailability.[9]

DFX frequently causes nausea, vomiting, diarrhea, and abdominal pain.[10]

According to the World Health Organization, adherence is the degree to which a person's attitude agrees with a medical staff's recommended course of action.[11]

The literature on adherence does not focus specifically on thalassemia populations. However, given that treatment is lifelong, adherence is a substantial problem.[10]

Adherence is a complicated phenomenon that encompasses interconnected elements linked to each patient's illness, therapy, and environment as well as psychological elements that all affect a patient's adherence to a recommended regimen. The effectiveness of treatment is greatly hampered by poor adherence.[2] In this paper, we evaluated ICT adherence among thalassemia major patients in Babylon province, Iraq, and sought to pinpoint the causes of subpar adherence.

Study design, sample, and setting

This analysis cross-sectional study was conducted on 100 β-thalassemia major patients who were registered at Babylon, Iraq, a hereditary blood disease center over a 2-month period from March 2023 to the end of April 2023.

Inclusion criteria

All patients with β-thalassemia major receiving chelation therapy were included in the study. Only DFX was available in the center at the time of study.

Exclusion criteria

Any patients who refused to participate in the study were excluded from the study.

Data collection tools

After their condition had stabilized, patients and/or their

parents or caregivers were questioned for 10–15 min using a premade questionnaire. Age, gender, marital status, education, occupation, place of residence, age at diagnosis, number of affected relatives, transfusion history, chelation therapy, chronic medication, and illness complications were among the information acquired. In addition, certain information was gathered from their center records, such as the most recent serum ferritin and pretransfusion packed cell volume (PCV) results.

Ethical considerations

Before being enrolled in the trial, the patient or their caretaker provided an informed verbal agreement. The study was also authorized by Babylon University's College of Medicine of Hammurabi Ethical Committee.

Statistical analysis

Utilizing the Statistical Package for the Social Sciences (SPSS) program version 23, IBM, Chicago, USA, a statistical summary and analysis of the quantitative data gathered were performed. Frequencies and percentages were used to represent descriptive statistics. Student's *t*-test was used for analysis of the parameter (continuous variable) and Chi-square test for assessment of different categorical data. Statistical significance was defined as $P = 0.05$.

Results

The total study sample included 100 patients with mean age ± standard deviation (14.93 ± 6.85) years, the age range between 3 and 35 years. 25% of patients their age was between 16-20 years, 22% between 11-15 years, 21% between 6-10 years. 61% of patients were male. The great majority (97%) were single. 59% of patients were below bachelor. 96% were unemployed and about half of the patients (51%) were rural, as shown in Table 1.

About the number of affected family members with thalassemia, 26% of patients had no affected family members, while 38% had only one, 26% had two and 10% of them had ≥3, as illustrated in Figure 1.

The great majority (92%) of them not use chronic medication other than chelating therapy and folic acid. Disease complications other than organomegaly present in 14% of patients that include hepatitis C infection and growth delay in 5% of patients, diabetes mellitus in 3%, and hypothyroidism in 1%, as shown in Table 2 and Figure 2.

More than three-quarters of patients (79%) have good adherence for chelating therapy, where 21 patients have poor adherence, as shown in Table 2 and Figure 3.

Number of patients with poor adherence to chelating therapy was 21%, reasons of poor adherence were nausea and vomiting in 8% of patients, bitter taste of chelating therapy in 3% of them, and other causes shown in Figure 4.

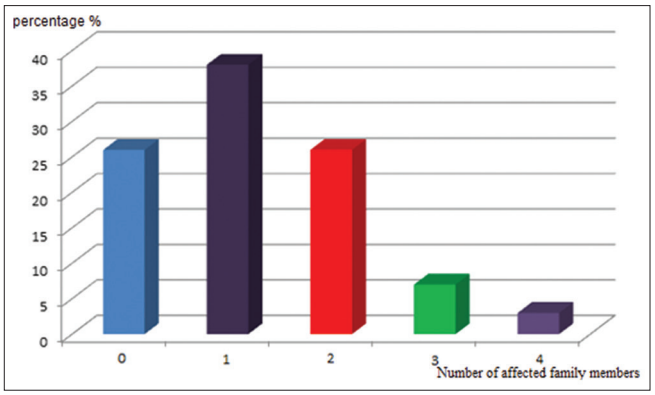

Figure 1: Number of affected family members among study population

Table 1: Demographic variables of the study sample (*n*=100)

	n (%)
Age (years)	
Mean±SD (range)	14.93±6.858 (3–35)
≤5	9
6–10	21
11–15	22
16–20	25
21–25	18
>25	5
Gender	
Male	61
Female	39
Marital status	
Single	97
Married	3
Education	
Under school age	14
Illiterate	26
Below bachelor	59
Bachelor	1
Occupation	
Unemployed	96
Employed	4
Residency	
Rural	51
Urban	49

SD=Standard deviation

Table 2: Disease-related variables of the study sample

Variable	*n* (%)
Chronic medication	
No	92
Yes	8
Complications	
No	86
Yes	14
Adherence	
No	21
Yes	79

The mean duration from diagnosis was 13.6 years, transfusion duration was 13.4 years, transfusion frequency was about 23 days, and chelating duration was 10.7 years.

The mean of PCV was 22%, while the mean of serum ferritin level was 4342 mg/dL.

There was a significant association between mean PCV of patients and their adherence to chelating therapy (P = 0.009), and other variables show nonsignificant association, as shown in Table 3.

Similarly, there was no significant correlation between patient's adherence to chelating therapy and patient's age, gender, residency, and complications of disease, as shown in Table 4.

Discussion

The study assessed the adherence of (100) thalassemia major patients taking ICT and found that 79% of them were adherent with treatment while 21% were not.

The most common cause of nonadherence was due to gastrointestinal side effects of the medications. The second common causes were due to disinterest and feeling hassled or the drug tasted bitter. Other causes were due to forgetfulness, some psychological issues, and taking other medications.

Assessing factors associated with poor adherence revealed nonsignificant effect for disease and chelation durations as well as transfusion frequency and duration. Age, gender, residence, and complications were also nonsignificantly affecting adherence.

Level of PCV was found to have a significant negative effect on adherence while serum ferritin level was not.

A study was conducted in Malaysia from 2019 to 2020 in which 70 patients were enrolled with 51.4% had good adherence with the remaining patients were nonadherent. Forgetfulness was the most common cause of poor adherence, factors like gender, patient educational level, and serum ferritin have no significant effect on adherence while family income had, a lesser number of participants were included in this study (70) with longer duration of data collection (1 year).[2]

In Turkey, a study was done to compare adherence with oral and parenteral iron chelation treatment, showed adherence to parenteral one from 59% to 78% and for oral one from 79% to 98% with age being one of the predictors of good adherence, higher in children than in adult, this study evaluated three different centers and include thalassemia intermedia and sickle cell disease patients in addition to thalassemia major one.[12]

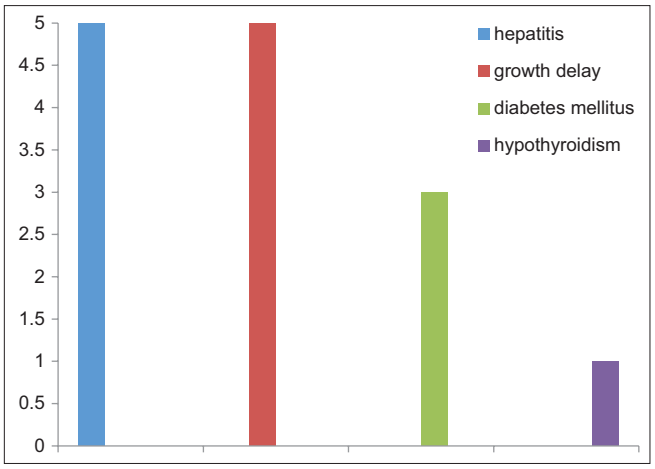

Figure 2: Disease complications of the study sample

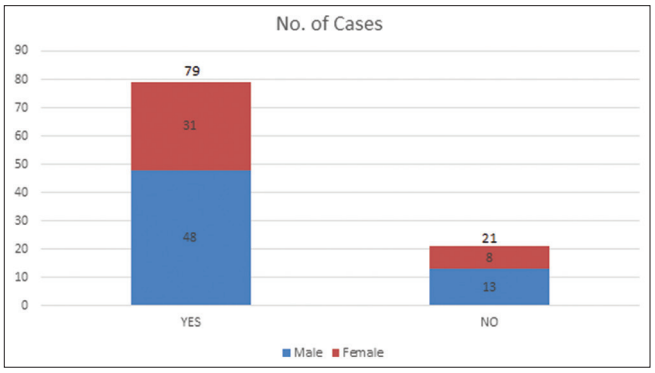

Figure 3: Adherence for chelation therapy

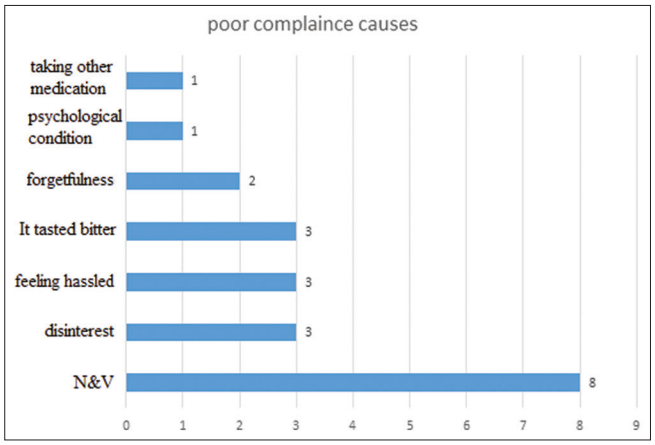

Figure 4: Causes of poor adherence (n = 21)

Another study was done by the thalassemia clinical research network which compared the adherence rate of DFO and DFX with an adherence rate of 90% versus 75% for both respectively. Adherence was better in children than in adults. Predictors of poor adherence were smoking, technical issues, and fewer transfusion history regarding DFO, while regarding DFX, poor adherence was associated with bodily pain and depression, while anxiety was associated with higher adherence rate.

Table 3: Transfusion-related variable and its correlation to adherence

Variable	Mean±SD	Minimum	Maximum	Correlation with adherence (*P*, using Student's *t*-test)
Duration from diagnosis (years)	13.6±6.9	2	35	0.391
Ferritin (mg/dL)	4342±3189	801	12,000	0.115
PCV	0.22±0.03	0.12	0.34	0.009
Transfusion duration (years)	13.4±6.8	1	35	0.319
Transfusion frequency (days)	22.8±9.4	7	60	0.109
Chelation duration (years)	10.7±6.5	1	32	0.307

SD=Standard deviation; PCV=Packed cell volume

Table 4: Correlation of adherence to other study variables

Variable	*n*	Adherence		*P* (using χ^2)
		No	Yes	
Age				
≤5	9	2	7	0.403
6–10	21	3	18	
11–15	22	5	17	
16–20	25	6	19	
21–25	18	3	15	
>25	5	2	3	
Gender				
Male	61	13	48	0.924
Female	39	8	31	
Residence				
Rural	51	9	42	0.406
Urban	49	12	37	
Complication				
No	86	18	68	0.966
Yes	14	3	11	

Switching from one type of chelation therapy to another was also evaluated by this study.[13]

One similar Indian study was conducted by Sidhu *et al*. with nonadherence rate of 10.7%, with serum ferritin level found to be higher in nonadherent patients. Factors associated with poor adherence were multi-drug therapy, younger age, and lower family income and support. There is no correlation between adherence and knowledge level, in this prospective study larger number of patients were enrolled and their adherence was assessed using Likert scale.[6]

A study in Egypt revealed an adherence rate of 78.2% with a mean serum ferritin level of 4623 mg/L.[14]

Another study in Jordan revealed an adherence rate of 73% among Jordanian adolescents with thalassemia major, the presence of sibling with thalassemia, lack of parental monitoring, lower family income, decrease frequency of blood transfusion, and psychological impairment were found significant predictors of nonadherence, white disease knowledge was not associated with adherence status.[15]

In Iran, a study was done correlating adherence with serum ferritin level with 18.2% adherence rate for those who had serum ferritin level of <2000 mg/L and 32.3% for those with serum ferritin level of 2000–4000 mg/L. Nonadherence was observed in 48.8% who had serum ferritin of more than 4000 mg/L. This study evaluated the adherence to deferoxamine chelation therapy.[16]

A study done in Ibrahim Bin Hamad Obaidullah Hospital, RAK, UAE, revealed a nonadherence rate of 67.85%, which was mainly affected by changing the route of administration of ICT, and it evaluated the effect of switching from one type of chelation therapy to another.[17]

In the present study, the serum ferritin level was high despite good adherence of patients, a similar result was found in a study done in Al Karama and Babylon Teaching Hospitals that explained by inadequate chelation due to shortage in chelation supply, use of agents from nonauthentic companies, and frequent shifting from one agents to another due to nonavailability.[18]

Conclusion

In general, thalassemia major patients in Babylon governorate have a good level of adherence to ICT which was nearly comparable or even better than adherence rates in other Middle East countries. Despite that, the chelation is inadequate due to logistic issues. However, measures to improve adherence and chelating agents more should be paid attention by the health centers.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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